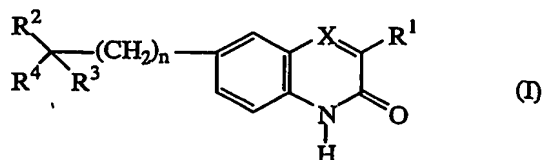


CLAIMS

1. A compound of formula (I),



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1 or 2;

X is N or CR^5 , wherein R^5 is hydrogen or taken together with R^1 may form a bivalent radical of formula $-CH=CH-CH=CH-$;

15 R^1 is C_{1-6} alkyl or thienyl;

R^2 is hydrogen or hydroxy or taken together with R^3 or R^4 may form $=O$;

R^3 is a radical selected from

- 20 $-(CH_2)_s-NR^6R^7$ (a-1),
 $-O-H$ (a-2),
 $-O-R^8$ (a-3),
 $-S-R^9$ (a-4), or
 $-C\equiv N$ (a-5),

25 wherein

s is 0, 1, 2 or 3;

R^6 is $-CHO$, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, piperidinyl C_{1-6} alkylaminocarbonyl, piperidinyl, piperidinyl C_{1-6} alkyl, piperidinyl C_{1-6} alkylaminocarbonyl, C_{1-6} alkyloxy, thienyl C_{1-6} alkyl, pyrrolyl C_{1-6} alkyl, aryl C_{1-6} alkylpiperidinyl, arylcarbonyl C_{1-6} alkyl, arylcarbonylpiperidinyl C_{1-6} alkyl, haloindazolylpiperidinyl C_{1-6} alkyl, or aryl C_{1-6} alkyl(C_{1-6} alkyl)amino C_{1-6} alkyl;

30 R^7 is hydrogen or C_{1-6} alkyl;

35 R^8 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl or di(C_{1-6} alkyl)amino C_{1-6} alkyl; and

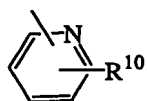
-39-

R^9 is di(C_{1-6} alkyl)amino C_{1-6} alkyl;
or R^3 is a group of formula

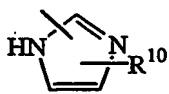


wherein

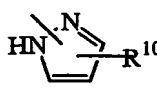
5 Z is a heterocyclic ring system selected from



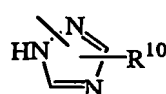
(c-1)



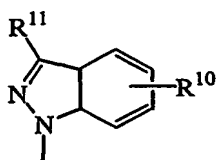
(c-2)



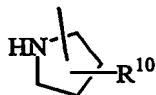
(c-3)



(c-4)



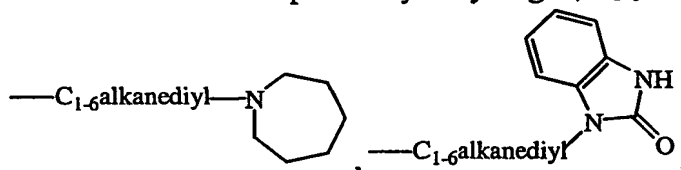
(c-5)



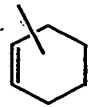
(c-6)

10

wherein each R^{10} independently is hydrogen, C_{1-6} alkyl, aminocarbonyl, hydroxy,



C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkylamino, aryl C_{1-6} alkyl,
di(phenyl C_{2-6} alkenyl), piperidiny C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl C_{1-6} alkyl,
15 aryloxy(hydroxy) C_{1-6} alkyl, haloindazolyl, aryl C_{1-6} alkyl, aryl C_{2-6} alkenyl, morpholino,
 C_{1-6} alkylimidazolyl, or pyridiny C_{1-6} alkylamino;

R^4 is hydrogen, C_{1-6} alkyl, furanyl, pyridiny C_{1-6} alkyl or  ;

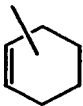
aryl is phenyl or phenyl substituted with halo, C_{1-6} alkyl or C_{1-6} alkyloxy;

20

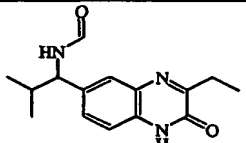
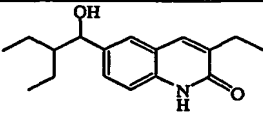
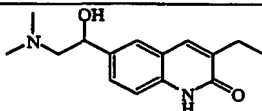
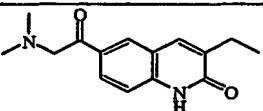
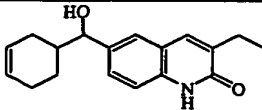
with the proviso that when

n is 0, X is N, R^2 is hydrogen, R^3 is a group of formula (b-1), Z is the heterocyclic
ring system (c-2) or (c-4) wherein said heterocyclic ring system Z is attached to the
rest of the molecule with a nitrogen atom, and R^{10} is hydrogen; then

25 R^4 is other than C_{1-6} alkyl or pyridiny C_{1-6} alkyl.

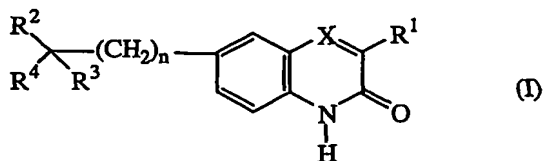
2. A compound as claimed in claim 1 wherein
 n is 0 or 1; X is N or CR⁵, wherein R⁵ is hydrogen; R³ is a radical selected from (a-1),
 (a-2) or (a-3) or is a group of formula (b-1) i.e. -Z-; s is 0, 1 or 2; R⁶ is -CHO, C₁-
 6alkyl, piperidinylC₁₋₆alkyl, arylcarbonylpiperidinylC₁₋₆alkyl or
 5 arylC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl; R⁸ is C₁₋₆alkyl; when R³ is a group of formula
 (b-1) then Z is a heterocyclic ring system selected from (c-2) or (c-4); and each R¹⁰
 independently is hydrogen, C₁₋₆alkyl or C₁₋₆alkyloxyC₁₋₆alkylamino.
3. A compound according to claim 1 and 2 wherein
 10 n is 0; X is N or CR⁵, wherein R⁵ is hydrogen; R¹ is C₁₋₆alkyl;
 R² is hydrogen or hydroxy or taken together with R⁴ may form =O; R³ is a radical
 selected from (a-1) or (a-2); s is 0 or 1; R⁶ is -CHO or C₁₋₆alkyl; and R⁴ is
 hydrogen, C₁₋₆alkyl or .

- 15 4. A compound according to claim 1, 2 and 3 wherein the compound is selected from
 compound No 1, compound No 5, compound No 7, compound No 3 and compound
 No 17.

 compound 1	 compound 5
 compound 7	 compound 3
 compound 17	

5. A compound as claimed in any of claims 1 to 4 for use as a medicine.
- 20 6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and
 as an active ingredient a therapeutically effective amount of a compound as claimed
 in claim 1 to 4.
- 25 7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein
 the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 4
 are intimately mixed.

8. Use of a compound for the manufacture of a medicament for the treatment of a PARP mediated disorder, wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1 or 2;

X is N or CR^5 , wherein R^5 is hydrogen or taken together with R^1 may form a bivalent radical of formula $-CH=CH-CH=CH-$;

15 R^1 is C_{1-6} alkyl or thienyl;

R^2 is hydrogen or hydroxy or taken together with R^3 or R^4 may form $=O$;

R^3 is a radical selected from

- 20 $-(CH_2)_s-NR^6R^7$ (a-1),
 $-O-H$ (a-2),
 $-O-R^8$ (a-3),
 $-S-R^9$ (a-4), or
 $-C\equiv N$ (a-5),

25 wherein

s is 0, 1, 2 or 3;

R^6 is $-CHO$, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkylcarbonyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylcarbonylamino C_{1-6} alkyl, piperidinyl C_{1-6} alkylaminocarbonyl, piperidinyl, piperidinyl C_{1-6} alkyl, piperidinyl C_{1-6} alkylaminocarbonyl, C_{1-6} alkyloxy, thienyl C_{1-6} alkyl, pyrrolyl C_{1-6} alkyl, aryl C_{1-6} alkylpiperidinyl, arylcarbonyl C_{1-6} alkyl, arylcarbonylpiperidinyl C_{1-6} alkyl, haloindazolylpiperidinyl C_{1-6} alkyl, or aryl C_{1-6} alkyl(C_{1-6} alkyl)amino C_{1-6} alkyl;

30 R^7 is hydrogen or C_{1-6} alkyl;

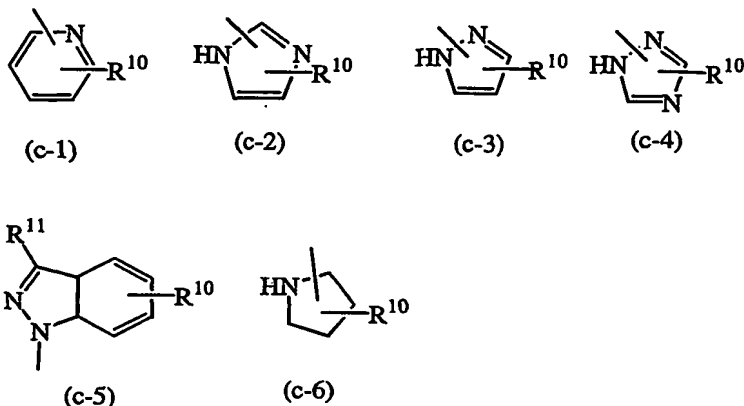
35 R^8 is C_{1-6} alkyl, C_{1-6} alkylcarbonyl or di(C_{1-6} alkyl)amino C_{1-6} alkyl; and

R^9 is di(C_{1-6} alkyl)amino C_{1-6} alkyl;
or R^3 is a group of formula



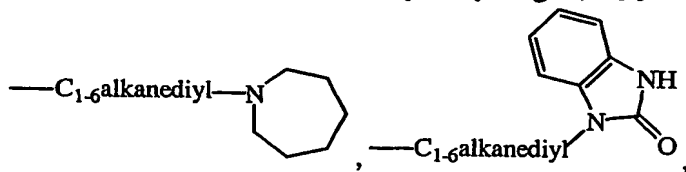
wherein

5 Z is a heterocyclic ring system selected from



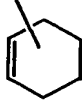
10

wherein each R^{10} independently is hydrogen, C_{1-6} alkyl, aminocarbonyl, hydroxy,



15

C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkylamino, aryl C_{1-6} alkyl,
di(phenyl C_{2-6} alkenyl), piperidiny C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl C_{1-6} alkyl,
aryloxy(hydroxy) C_{1-6} alkyl, haloindazolyl, aryl C_{1-6} alkyl, aryl C_{2-6} alkenyl, morpholino,
 C_{1-6} alkylimidazolyl, or pyridiny C_{1-6} alkylamino;

R^4 is hydrogen, C_{1-6} alkyl, furanyl, pyridinyl, aryl C_{1-6} alkyl or  ;

aryl is phenyl or phenyl substituted with halo, C_{1-6} alkyl or C_{1-6} alkyloxy.

20

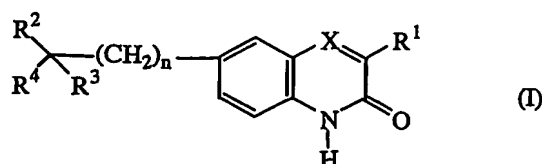
9. Use according to claim 8 of a PARP inhibitor of formula (I) for the manufacture of
a medicament for the treatment of a PARP-1 mediated disorder

10. Use according to claim 8 and 9 wherein the treatment involves chemosensitization.

25

11. Use according to claim 8 and 9 wherein the treatment involves radiosensitization.

12. A combination of a compound with a chemotherapeutic agent wherein said compound is a compound of formula (I)



5

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

10

X is N or CR⁵, wherein R⁵ is hydrogen or taken together with R¹ may form a bivalent radical of formula -CH=CH-CH=CH-;

R¹ is C₁₋₆alkyl or thienyl;

15

R² is hydrogen or hydroxy or taken together with R³ or R⁴ may form =O;

R³ is a radical selected from

- 20
- (CH₂)_s- NR⁶R⁷ (a-1),
 - O-H (a-2),
 - O-R⁸ (a-3),
 - S- R⁹ (a-4), or
 - C≡N (a-5),

wherein

25

s is 0, 1, 2 or 3;

R⁶ is -CHO, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkylcarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylcarbonylaminoC₁₋₆alkyl, piperidinylC₁₋₆alkylaminocarbonyl, piperidinyl, piperidinylC₁₋₆alkyl, piperidinylC₁₋₆alkylaminocarbonyl, C₁₋₆alkyloxy, thienylC₁₋₆alkyl, pyrrolylC₁₋₆alkyl, arylC₁₋₆alkylpiperidinyl, arylcarbonylC₁₋₆alkyl, arylcarbonylpiperidinylC₁₋₆alkyl, haloindozolylpiperidinylC₁₋₆alkyl, or arylC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl;

30

R⁷ is hydrogen or C₁₋₆alkyl;

R⁸ is C₁₋₆alkyl, C₁₋₆alkylcarbonyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl; and

35

R⁹ is di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

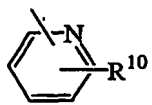
or R³ is a group of formula



wherein

Z is a heterocyclic ring system selected from

5



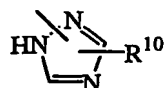
(c-1)



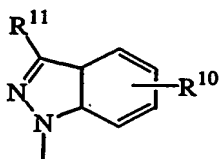
(c-2)



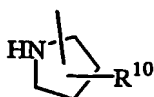
(c-3)



(c-4)

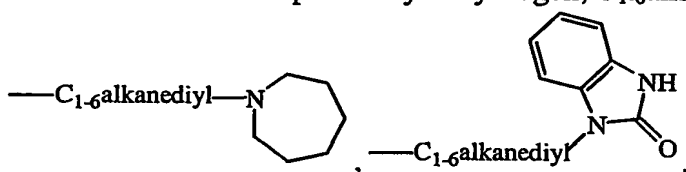


(c-5)



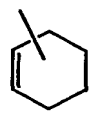
(c-6)

10 wherein each R¹⁰ independently is hydrogen, C₁₋₆alkyl, aminocarbonyl, hydroxy,



C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkylamino, arylC₁₋₆alkyl,
di(phenylC₂₋₆alkenyl), piperidinyC₁₋₆alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkylC₁₋₆alkyl,
aryloxy(hydroxy)C₁₋₆alkyl, haloindazolyl, arylC₁₋₆alkyl, arylC₂₋₆alkenyl, morpholino,
15 C₁₋₆alkylimidazolyl, or pyridinyC₁₋₆alkylamino;

R⁴ is hydrogen, C₁₋₆alkyl, furanyl, pyridinyl, arylC₁₋₆alkyl or

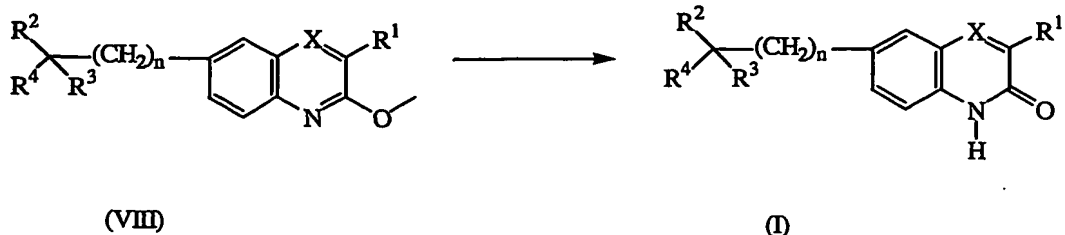


aryl is phenyl or phenyl substituted with halo, C₁₋₆alkyl or C₁₋₆alkyloxy.

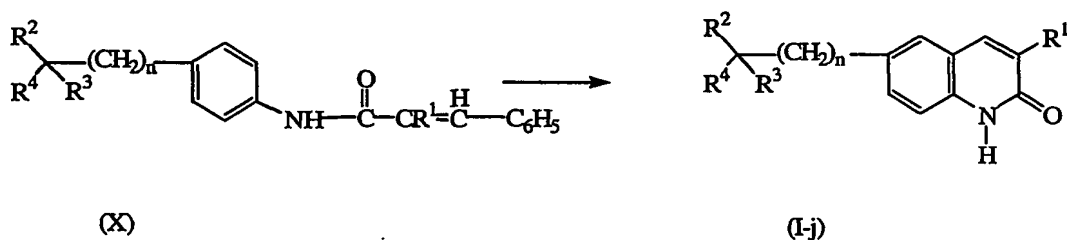
20 13. A process for preparing a compound as claimed in claim 1, characterized by
a) the hydrolysis of intermediates of formula (VIII), according to art-known methods,
by submitting the intermediates of formula (VIII) to appropriate reagents, such as,
tinchloride, acetic acid and hydrochloric acid, in the presence of a reaction inert
solvent, e.g. tetrahydrofuran.

25

-45-



b) the cyclization of intermediates of formula (X), according to art-known cyclizing procedures into compounds of formula (I) wherein X is CH herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents.



c) the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) wherein R^h is C₁₋₆alkyl, into compounds of formula (I), wherein X is N, herein referred to as compounds of formula (I-i), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like.

